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<p>(21) International Application Number: PCT/EP95/01162 (22) International Filing Date: 28 March 1995 (28.03.95) (30) Priority Data: 9406255.1 29 March 1994 (29.03.94) GB (71) Applicant (for all designated States except US): ELEC-TROSOLS LIMITED [GB/GB]; Thursley Copse, Farnham Lane, Haslemere, Surrey GU27 1HA (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): COFFEE, Ronald, Alan [GB/GB]; Electrosols Limited, Thursley Copse, Farnham Lane, Haslemere, Surrey GU27 1HA (GB). (74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).</p>		<p>(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: DISPENSING DEVICE</p> <p>(57) Abstract</p> <p>A device for dispensing a liquid for inhalation, which comprises an unshielded electrohydrodynamic comminution means (1), a means for supplying a liquid to the comminution means, a sharp discharge electrode (12) and, optionally, a means for charging the discharge electrode to a polarity opposite to that of the comminution means, wherein the discharge electrode is located so as to direct gaseous ions into the body of the comminuted liquid and thereby to fully or partially discharge the comminuted liquid.</p> <div data-bbox="1052 1129 1365 1890"></div>		

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DISPENSING DEVICE

5 The invention relates to a dispensing device for comminuting a liquid and the use of such a device, in particular, in medicine.

Dispensing devices are known which produce a finely divided spray of liquid droplets by electrostatic (more properly referred to as 'electrohydrodynamic') means. The droplet spray in such devices is generated by applying an electric field to a liquid at a spray head or spray edge. The
10 strength of the electric field is sufficiently high to provide comminution of the liquid from the spray head. The droplets produced are electrically charged and thus are prevented from coagulating by mutual repulsion.

United Kingdom patent number 1569707 describes an electrohydrodynamic spray device principally for use in crop spraying. An
15 essential component of the GB 1569707 spray device is a field intensifying electrode, cited adjacent the spray head. The field intensifying electrode is stated to reduce the incidence of corona discharge and allows lower electric field strengths to be used during spray generation.

US 4801086 discloses an electrohydrodynamic spray device which
20 produces multiple spray streams.

United Kingdom patent number 2018627B discloses an electrohydrodynamic spray device wherein the droplet spray is fully or partially discharged by means of an earthed electrode having a sharp or pointed edge and located downstream of the spray head. The GB 2018627B spray device does
25 not comprise the field intensifying electrode of GB 1569707.

European Patent number 0234842 discloses an inhaler which uses electrohydrodynamic spray technology. In use, the spray of charged droplets is discharged prior to inhalation by means of a sharp discharge electrode carrying an opposite charge to the droplet spray and located downstream of the spray
30 head. The droplets are discharged to facilitate droplet deposition into the respiratory tract by preventing deposition of charged droplets onto the mouth and throat of the user. The EP 0234842 spray device does not comprise the field intensifying electrode of GB 1569707.

An essential requirement of the EP 0234842 electrohydrodynamic
35 inhaler is a neutral shield electrode which is stated to be required to prevent the

corona from the sharp discharge electrode from adversely affecting the formation of the spray. It has now surprisingly been discovered that a shield electrode is not required for effective spray discharge or partial discharge.

Accordingly, the present invention provides a device for dispensing a
5 liquid for inhalation, which comprises an unshielded electrohydrodynamic
comminution means, a means for supplying a liquid to the comminution means,
a sharp discharge electrode and, optionally, a means for charging the discharge
electrode to a polarity opposite to that of the comminution means, wherein the
discharge electrode is located so as to direct gaseous ions into the body of the
10 comminuted liquid and thereby to fully or partially discharge the comminuted
liquid.

A further optional component of the present device is a field guard
electrode located so as to regulate the amount the comminuted liquid is
discharged by the discharge electrode. One particular field guard electrode,
15 suitably an annular electrode, is arranged to effect such regulation by adjustably
altering the effective shape of the discharge electrode, for example by adjustably
enclosing or surrounding the discharge electrode, favourably by a screw thread
adjustment means.

The device of the invention may be adapted into any embodiment form
20 which dispenses comminuted liquid for inhalation, for medicinal and non-
medicinal use.

A suitable non-medicinal use includes the dispensing of a perfume or an
aromas.

A suitable non-medicinal use includes the dispensing of a biocide or an
25 insecticide.

Preferably, the device is in the form of an inhaler, for the inhaled
delivery of a medicament.

Suitably the device is adapted to be portable.

A preferred liquid is a liquid medicament formulation adapted for
30 inhaled administration.

Medicaments suitable for adaption for inhaled administration include those
used for the treatment of disorders of the respiratory tract, such as reversible
airways obstruction and asthma and those used in the treatment and/or
prophylaxis of disorders associated with pulmonary hypertension and of
35 disorders associated with right heart failure by inhaled delivery.

The electrohydrodynamic comminution means may be any conventional electrohydrodynamic comminution means, for example those described in the above mentioned patent specifications.

Suitable liquid formulations include medicament formulations, perfume or aroma formulations.

Suitably, the comminution means comprises a comminution surface or edge and means for electrically charging the liquid at the said surface or edge to a potential sufficient to provide comminution of the liquid, the potential usually being of the order of 1-20 kilovolts.

One comminution surface or edge is provided by the end surface of a bundle of fibres, the fibres being so aligned that liquid flows along the length of the fibres and between the interstitial spaces defined by the fibres to the said end surface.

Suitable fibres are fibres of ceramic, such as glass, or polymer such as polyester or nylon.

A preferred comminution surface or edge is provided by a thin capillary tube or a slot defined by two parallel plates or concentric tubes.

The means for supplying a liquid formulation to the comminution means may be any appropriate mechanical or electrical liquid supplying means such as a syringe pump or an electrically powered pump as described in EP 0029301.

The comminution means of the dispenser provides liquid droplets within the range of from 0.1 to 500 microns in diameter, more usually from 1.0 to 200 microns and preferably, for topical application, diameters in the range of from 5.0 to 100 microns.

For a given liquid the diameter of the droplets can be controlled by varying the applied voltage and liquid flow rate using routine experimental procedures. However, liquids having viscosities within the range of from 1 to 500 centipoise and resistivities in the range of from 10^2 - 10^8 ohm m can be comminuted by the present device.

The device described will produce electrically charged droplets of accurately controlled sizes which may then be used to deliver drugs to the pulmonary membranes by inhalation, or to the blood stream by inhalation to the terminal airways. Currently available aerosol generators commonly used for medical purposes, such as, for example, asthma aerosol droplet or powder delivery units, have generally a polydisperse nature. That is to say that the

droplet or particle size range produced by ordinary aerosol generators will contain sizes above and below those believed to be optimally beneficial in any medical drug delivery operation. For example, asthma dispensers often have more than ninety percent of the volume of drug delivered at diameters greater than 10.0 μm . It is believed that the droplets or particles of such diameters will not enter the middle airways of the lung, where they are required, and will thus be imbibed by the patient through the upper airways, with little or no therapeutic result, and with possible side effects. Also, droplets or particles of less than about 1.00 μm may be present and may flow through to the terminal airways, where they could be rapidly systemically imbibed, thus also risking side effects, without therapeutic benefit.

The ideal droplet dispenser for delivery of medicament to the lower respiratory tract would be able to produce droplets in very narrow (monodisperse) size spectra, say all below 10.0 μm . It would be better still if all droplets could be made to be within a range of ± 25 percent or better, with average size controllable anywhere in the range of 0.1 μm to 10.00 μm , especially 3 μm to 10.00 μm for inhalation therapy. Further benefits would accrue if the same device could process reactive fluid mixtures by use of electric field turbulence at the instant of spraying droplets, so that no reaction could take place before application.

As described above electrohydrodynamic spray devices are known which produce multiple spray streams. However such devices are not known to be applied to the administration of liquid formulations for inhalation. Accordingly, there is provided an electrohydrodynamic dispensing device for liquid formulations for inhalation which comprises a mixing nozzle as described in USP4801086.

Thus, by inducing electric field turbulence, two or more liquid components can be mixed at the moment of delivery. This is an essential requirement for ingredients which would react too early if premixed. By reacting too soon before application, they may lose their intended properties or, for example the mixture may increase its viscosity so as to become unsprayable. Such an instantaneous mixing facility at the point and time of application of the mixture has not previously been possible.

The process of droplet production may require total, or partial discharge of droplets when used for inhalation. A zero charge ensures that droplets are

deposited into the required respiratory area or areas, by mass differentiation, in accordance with the agreed opinion, as published in the medical literature (see "Inhalation Studies" edited by R.F. Phalen, published by CRC Press, 1984). Additionally, by retaining a specific, generally reduced charge, it may be possible to further increase the specificity of the zone of deposition within the respiratory system.

When used herein 'unshielded electrohydrodynamic comminution means' relates to a comminution means which does not have a neutral shield electrode as defined in EP 0234842.

When used herein 'medicament' includes proprietary medicines, pharmaceutical medicines and veterinary medicines.

When used herein, unless more specifically defined herein, 'inhaled administration' includes administration to and via the upper respiratory tract, including the nasal mucosa, and the lower respiratory tract.

The liquid medicinal formulations for use in the device of the invention may be formulated according to conventional procedures, such as those disclosed in the US Pharmacopoeia, the European Pharmacopoeia, 2nd Edition, Martindale The Extra Pharmacopoeia, 29th Edition, Pharmaceutical Press and the Veterinary Pharmacopoeia.

The liquid perfume or aroma formulations for use in the device of the invention may be formulated according to conventional procedures, such as those disclosed in Harry's Cosmeticology, 9th Edition, 1982, George Goodwin, London.

Specific Description of the Devices and Processes of the Invention

(1) Nozzles

Figure 1 shows a thin-walled capillary tube (1), made of conducting, semiconducting or electrically insulating material and electrically connected to a source of high-voltage direct-current, either directly or through the liquid. A single jet (3) is produced from a cusp (2) of liquid, both of which form naturally, according to the voltage and flow rate for a given liquid. Fig. 2 shows a conducting, semiconducting or insulating cylinder (1) which may have a larger diameter than those shown in fig. 1. This nozzle has an inner-member, (4) which is approximately coaxial with the outer tube, (1). Fig. 3 shows a slot

nozzle, formed between two parallel plates (2) having conducting, semiconducting or insulating edges electrically connected to a high-voltage direct-current supply, from which the liquid emerges, forming cusps and jets when the voltage supply and liquid flow rates are suitably adjusted according to the type of liquid being sprayed. For a given jet (and thus droplet) size, and a given liquid, this nozzle may enable a higher flow rate to be achieved than those in which a single cusp and jet are used.

(2) Flow Inducers

10 An example of such a device is that illustrated in Fig. 4 which shows an ion stream flow inducer, wherein a high voltage electrode (5) breaks up pairs of charge carriers within the liquid, thus neutralizing those of opposite polarity at the electrode, and leaving a large population of monionized like-polarity charge carriers which stream away from the high voltage electrode by coulombic force, thus moving the liquid in the direction of the counter electrode (6) by means of viscous drag. This pumping means requires that an electrode (5) is able to effectively inject like-polarity charge carriers into the liquid, close to the electrode (5). This may be effectively done by using a sharp-edged conducting or semiconducting surface, held at a sufficiently high potential to disrupt lightly bonded charge carriers or to ionize the liquid. Normally, it is only possible to establish a strong enough field for both creating unipolar charge carriers and pumping the liquid, when the liquid is of sufficient resistivity. Typically a resistivity of, say 10 (exp. 8) ohm meters, will pump at several millilitre per minute, with a head of up to one meter, at a voltage of 10 to 20 kilovolts, and a direct current of only a few microamperes. More conductive liquids will draw more current and will establish a weaker electric field. Thus highly conducting liquids, such as, say tap water may not readily establish a practicable drag pressure.

30 (3) Reactive Liquid Mixing

Two or more liquids may be mixed after emerging from the nozzle by maximizing turbulent motion which can be induced within the cusp (2) which forms the base of each liquid jet (3). Fig. 5 shows a nozzle formed by three parallel plates, forming two slot-gaps (7) through which two liquids, a and b, are induced to flow, and to subsequently become mixed in the cone-shaped

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liquid base (2) of each jet, in accordance with eddy currents that can be induced as shown. This mixing may be maximized by using a liquid formulation having the lowest possible viscosity for each liquid; the maximum nozzle potential; and an optimal flow rate and degree of asymmetry of the individual flow rates of the component liquids.

An alternative to the mixing arrangement of fig. 5 is shown in cross section in fig. 6, in which two coaxial cylinders (8) and (9) form two flow-channels (13) and (11). This arrangement has advantages and may induce a greater degree of mixing in some cases, for example, when there is a significant disparity in the flow rates of liquids a and b.

(4) Discharging Device

For delivering droplets into the middle and lower respiratory system, it is important that droplets are fully, or partially electrically discharged.

It has been found readily possible to discharge the droplets by one or both of two techniques, shown in fig. 7. The first method, uses one or more earthed sharp-edged conductors or semiconductors (12) suitably located downstream of the jets, so that an opposite polarity charge is induced at the said edge. If the nozzle (or other electrode) potential and/or the space charge density of the spray cloud (13) is sufficient then the induced charge, and hence the field strength, at the edge will be sufficient to break down the surrounding gas, thus producing a large population of like-polarity gas ions which will be accelerated away from the edge, toward the cloud of charged droplets. The mobility of the gaseous ions is much greater than that of the charged droplets, and the droplets may thus become largely or totally neutralized by bombardment with opposite-polarity ions. Alternatively, an electrode of like polarity to the nozzle may be used to induce gas-ion generation at the sharp electrode.

The above described method, shown in cross section in fig. 7 uses a passive electrode, which is the simplest method that we have found appropriate. However, it is dependent upon the nozzle or other like-polarity electrode or the droplet spray cloud having sufficient charge density to induce an air breakdown field (approximately 3 Mvolts/m). It may sometimes be preferred to connect the electrode (12) to earth through a source of d.c. high voltage, ensuring that the polarity is opposite to that of the spray cloud (13).

In each of the above devices, adjustment of the rate of ion bombardment may be provided by use of a field guard electrode (14) the controlling effect of which may be adjusted by screw positioning, to increase or decrease the flow of gas ions to the spray and/or by the use of other electrodes of like polarity to the
5 nozzle.

In these charge neutralization processes, opposite polarity gas ions bombard the charged droplets thus neutralizing them. In order to prevent these highly mobile gas ions from neutralizing the jets (3) or their respective cusps (2), before droplets, have been produced, it is preferable to direct the gas ions
10 only, or predominantly, toward the comminuted matter.

Claims

1. A device for dispensing a liquid for inhalation, which comprises an unshielded electrohydrodynamic comminution means, a means for supplying a liquid to the comminution means, a sharp discharge electrode and, optionally, a means for charging the discharge electrode to a polarity opposite to that of the comminution means, wherein the discharge electrode is located so as to direct gaseous ions into the body of the comminuted liquid and thereby to fully or partially discharge the comminuted liquid.
2. A device according to claim 1, wherein a field guard electrode is located so as to regulate the amount the comminuted liquid is discharged by the discharge electrode.
3. A device according to claim 2, wherein the field guard electrode, is arranged to effect such regulation by adjustably altering the effective shape of the discharge electrode by adjustably enclosing or surrounding the discharge electrode.
4. A device according to claims 2 or 3, wherein the field guard electrode is an annular electrode,
5. A device according to any one of claims 1 to 5, in the form of an inhaler.
6. A device according to claim 1, adapted to dispense a biocide or an insecticide.
7. A device according to claim 1, adapted to dispense a perfume or an aroma.

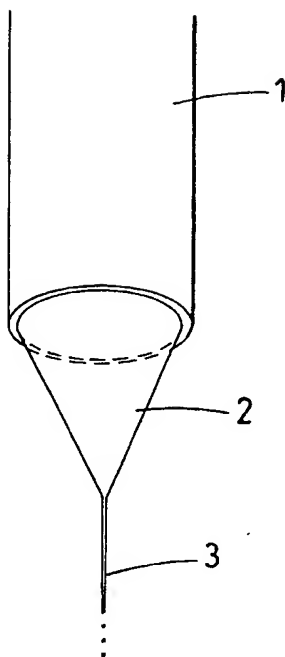


Fig. 1

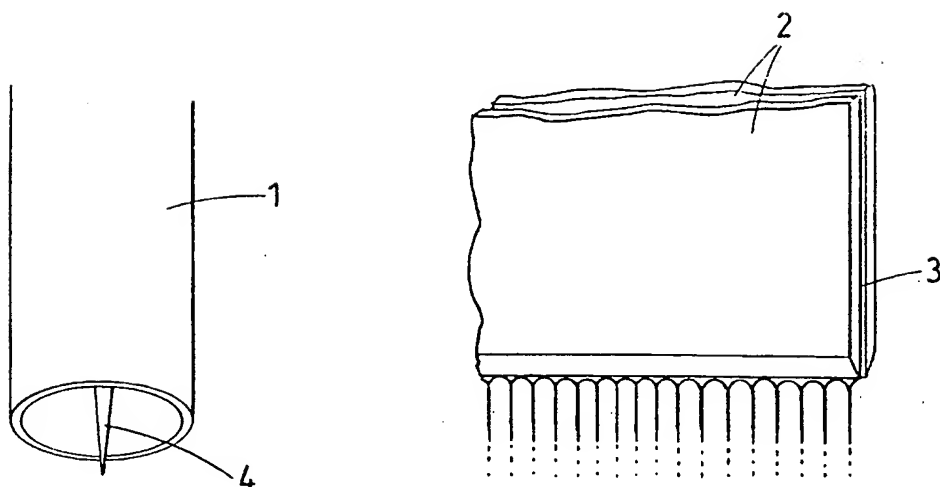


Fig. 2

Fig. 3

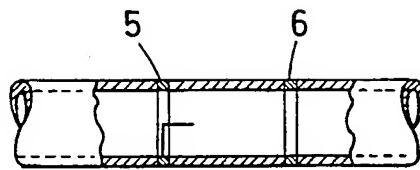


Fig. 4

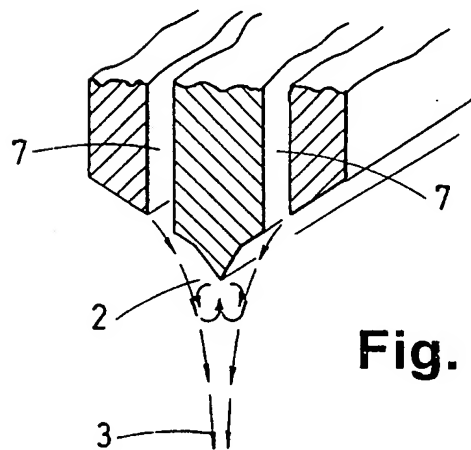


Fig. 5

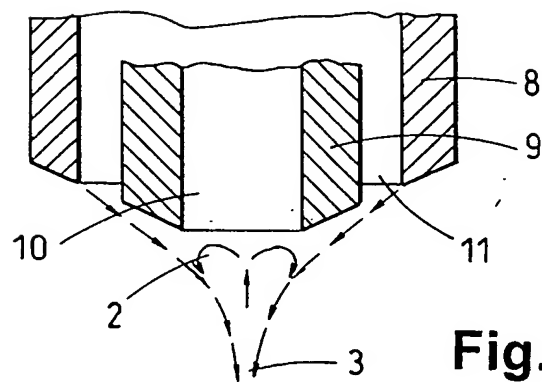


Fig. 6

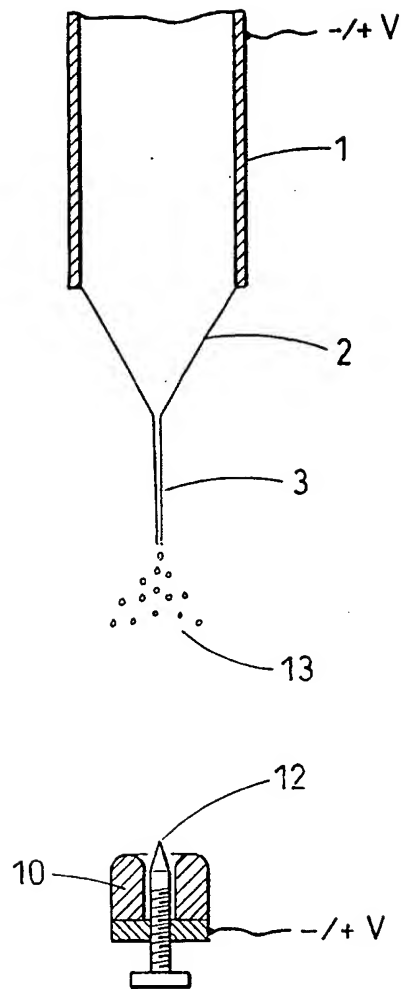


Fig. 7

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 95/01162

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 B05B5/053 B05B5/025

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B05B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 018 627 (ICI) 24 October 1979 cited in the application see page 2, line 97 - page 3, line 75; figures 2,5 ---	1-4
X	DE,A,41 06 564 (BOSCH) 3 September 1992 see the whole document ---	1
X	EP,A,0 250 164 (ICI) 23 December 1987 see claims 4,6; figure 1 ---	1
A	US,A,5 267 555 (PAJALICH) 7 December 1993 see abstract; figure 1 ---	5
A	EP,A,0 523 963 (UNILEVER N.V.) 20 January 1993 see claims 16,24 -----	6,7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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